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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
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Additional inventors are being named on the _____ *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

COADMINISTRATION OF RADIATION AND RSR13 FOR THE TREATMENT OF CANCER

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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OR

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 17 ☐ CD(s), Number _____

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☐ Application Date Sheet. See 37 CFR 1.76

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☑ Applicant claims small entity status. See 37 CFR 1.27.

☑ A check or money order is enclosed to cover the filing fees.

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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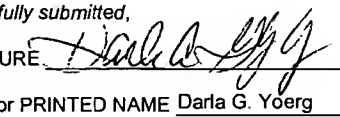
☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE 

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Date 4/22/04

REGISTRATION NO. 48,053 *(if appropriate)*

Docket Number: ALL.07/PR

TELEPHONE 303-268-0066

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

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COADMINISTRATION OF RADIATION AND RSR13 FOR THE TREATMENT OF CANCER

FIELD OF THE INVENTION

The invention relates to treatment of cancer, more particularly to coadministration of efaproxiral sodium (RSR13), supplemental oxygen, and radiation for treatment of cancer.

BACKGROUND OF THE INVENTION

The brain, cranial nerves, leptomeninges, spinal cord, and eye compose the central nervous system (CNS) and are at risk for the development of metastases from cancers. Chang & Lo, Diagnosis and Management of Central Nervous System Metastases from Breast Cancer, (2003) *The Oncologist*, 8:398–410. The disclosure of Chang & Lo, and all other patents, patent applications, and publications referred to herein are incorporated by reference herein in their entirety. Multiple, large autopsy series suggest that, in order of decreasing frequency, lung, breast, melanoma, renal, and colon cancers are the most common primary tumors to metastasize to the brain. Conventional treatment is aimed at palliation of symptoms and preservation of neurologic function. Conventional whole brain radiation therapy has been the mainstay of palliative treatment for brain, cranial nerve, spinal cord, and ocular metastases. Other treatment options for brain metastases include surgery to resect brain metastases, and stereotactic radiosurgery (SRS) to focally irradiate metastases. Ongoing research is aimed at refining criteria to select which patients with brain metastases should undergo surgery and SRS and how these focal therapies should be optimally integrated with whole-brain radiotherapy. Despite advances in neuroimaging, surgery, and radiation therapy, novel treatments are needed to improve the effectiveness of treatments for CNS metastases.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the dosing algorithm for RSR13 on Day 1 of RT.

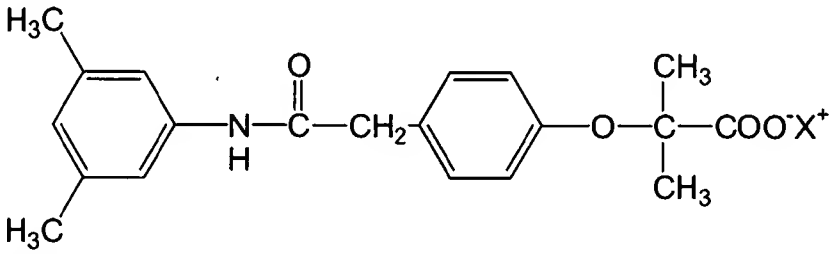
Figure 2 shows the dosing algorithm for RSR13 on Day 2 of RT.

Figure 3 shows the dosing algorithm for RSR13 on Days 3-10 of RT.

DETAILED DESCRIPTION OF THE INVENTION

It has been discovered that RSR13 may be administered, together with radiation and supplemental oxygen, in the treatment of cancers of the central nervous system, wherein the supplemental oxygen, radiation and RSR13 are administered in amounts effective to treat the cancer of the central nervous system in the host. Generally, an effective amount is an amount effective to either (1) reduce the symptoms of the disease sought to be treated or (2) induce a pharmacological change relevant to treating the disease sought to be treated. For cancer, an effective amount includes an amount effective to: reduce the size of a tumor; slow the growth of a tumor; prevent or inhibit metastases; increase the life expectancy of the affected individual; or improve the quality of life of the affected individual.

RSR13 2-[4-(((3,5-dimethylanilino)carbonyl)methyl)phenoxy]-2-methylpropionic acid):



is an allosteric effector of hemoglobin, and has been shown to enhance tissue oxygenation in vivo. Sometimes, RSR13 is represented by the name 2-[4-[2-[(3,5-dimethylphenyl)amino]-2-oxoethyl]phenoxy]-2-methylpropanoic acid. In general RSR13 is administered as a physiologically acceptable salt, such as the monosodium salt; that is, X+ is Na+. RSR13 induces allosteric modification of hemoglobin, such that its binding affinity for oxygen is decreased, resulting in increased oxygen distribution to tissues by erythrocytes.

The ability to allosterically modify hemoglobin also allows the compounds to be useful in treating a variety of disorders and conditions mediated through allosterically modifying hemoglobin to shift oxygen equilibrium in favor of free oxygen. Such disorders may include, but are not limited to, whole body or tissue hypothermia, hypoxia

or hypotension, wounds, brain injury, diabetic ulcers, chronic leg ulcers, pressure sores, tissue transplants, stroke or cerebro ischemia, ischemia or oxygen deprivation, respiratory disorders including acute respiratory distress syndrome and chronic obstructive pulmonary disorder, surgical blood loss, sepsis, multi-system organ failure, normovolemic hemodilution procedures, carbon monoxide poisoning, bypass surgery, carcinogenic tumors, oxygen deprivation of a fetus. The compound is useful in a method comprising the step of administering to a patient suffering from or undergoing the claimed condition a sufficient quantity of an allosteric effector compound. In the case of carcinogenic tumors, the compound is useful as a radiosensitizer in conjunction with ionizing radiation (See Teicher, (1996) *Drug Dev. Res.* 38:1-11; Rockwell and Kelley (1998) *Rad. Oncol. Invest.* 6:199-208; and Khandelwal et al. (1996) *Rad. Oncol. Invest.* 4:51-59). The allosteric modification properties also allow it to be useful in certain imaging methods, especially blood oxygen level dependent MRI, and also in diagnostic methods, including determination of tumor oxygenation, and determination of an optimal time for commencing radiation treatment based on tumor oxygenation. The preparation and uses for 2-[4-[2-[(3,5-dimethylphenyl)amino]-2-oxoethyl]phenoxy]-2-methyl-propionic acid and its physiologically acceptable salts has been described previously in U.S. Patent Numbers 5,049,695; 5,122,539; 5,290,803; 5,432,191; 5,525,630; 5,648,375; 5,661,182; 5,677,330; 5,705,521; 5,872,888; and 5,927,283, and U.S. Patent Application Publication No. 20030017612 A1. These patents also describe the preparation and use of structurally similar compounds. Other patents describing closely related compounds include 5,248,785; 5,731,454. These patents, applications, and all other patents, applications, and publications referred to herein, are specifically incorporated by reference herein.

In general, the invention provides a course of whole brain radiation therapy (WBRT) with supplemental oxygen and RSR13. In one embodiment, the WBRT is a multi-day, fractionated course of WBRT. In one embodiment, the course is a 10-day course. In one embodiment, RSR13 is received within about 30 minutes prior to daily WBRT and supplemental oxygen. In this embodiment, RSR13 administration with supplemental oxygen begins on the first day of RT (RT day 1) and will continue every RT day during the 10-day course of WBRT, for a total of 10 doses.

In general, RSR13 is administered in an initial dose of about 75-100 mg/kg. In one embodiment, subsequent doses of RSR13 are 75-100 mg/kg. In another embodiment, subsequent doses of RSR13 are determined with reference to standard cutaneous pulse oximetry (SpO_2) and the presence of adverse effects. The RSR13 dose may be lowered to 0-75 mg/kg if unacceptable nausea, vomiting, hypoxemia, or low SpO_2 events are observed. The RSR13 dose may be increased to 75-100 mg/kg if the SpO_2 is normal, at baseline or improved, and no unacceptable nausea, vomiting, or hypoxemia events occurred on the previous day.

In one embodiment, the invention provides a 10-day course of WBRT with supplemental oxygen and RSR13, wherein the RSR13 is administered as shown in Figure 1 on RT day 1, and is administered as shown in Figure 2 on RT day 2-10.

Patients treated with RSR13 received supplemental oxygen via a mask or nasal cannula. RSR13 decreases hemoglobin oxygen binding affinity and reduces oxygen loading in the lungs at ambient oxygen pressure. Without being bound by theory, it is believed that the administration of supplemental oxygen serves to optimize both hemoglobin oxygen saturation and tumor oxygenation, and to assure pulmonary oxygen uptake. In one embodiment, supplemental oxygen is administered for at least about 30 minutes prior to, during, and for at least 15 minutes after completion of daily WBRT. In one embodiment, the dose of supplemental oxygen is 4L/minute. In another embodiment, the dose of supplemental oxygen is adjusted as needed to maintain and SpO_2 measurement of greater than or equal to 90% during and after RSR13 administration. The oxygen may be 100% oxygen, carbogen, or other suitable exogenous oxygen source.

Radiation may be administered in a variety of fashions. For example, radiation may be electromagnetic or particulate in nature. Electromagnetic radiation useful in the practice of this invention includes, but is not limited, to x-rays and gamma rays. Particulate radiation useful in the practice of this invention includes, but is not limited to, electron beams, protons beams, neutron beams, alpha particles, and negative pi mesons. The radiation may be delivered using conventional radiological treatment apparatus and methods, and by intraoperative and stereotactic methods. Additional discussion regarding radiation treatments suitable for use in the practice of this invention may be

found throughout Steven A. Leibel et al., TEXTBOOK OF RADIATION ONCOLOGY (1998) (publ. W. B. Saunders Company), and particularly in Chapters 13 and 14. Radiation may also be delivered by other methods such as targeted delivery, for example by radioactive "seeds," or by systemic delivery of targeted radioactive conjugates. J. Padawer et al., Combined Treatment with Radioestradiol lucanthone in Mouse C3HBA Mammary Adenocarcinoma and with Estradiol lucanthone in an Estrogen Bioassay, *Int. J. Radiat. Oncol. Biol. Phys.* 7:347-357 (1981). Other radiation delivery methods may be used in the practice of this invention.

The amount of radiation delivered to the desired treatment volume may be variable. In one embodiment, radiation may be administered in amounts effective to cause the arrest or regression of the cancer of a central nervous system in a host, when the radiation is administered with RSR13 and supplemental oxygen. In one embodiment, radiation is administered in at least about 3 Gray (Gy) fractions at least once per day for five days per week, over ten days, to a treatment volume of up to about 30 Gray (GY). In other embodiments, different fractionated radiation schemes known to those skilled in the art are deployed such as 20 administrations of 2 Gy fractions or 15 administrations of 2.5 Gy fractions.

When irradiating the whole brain, a maximum dosage of 30 Gy is recommended. In one embodiment, radiation is administered to the whole brain of a host, wherein the host is being treated for metastatic cancer. In one embodiment, radiation is administered as soon as possible, or about within 30 minutes maximum, post-end RSR13 administration.

It will be apparent to those skilled in the art that various modifications and variations can be made in the methods of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents. Additionally, the following examples are appended for the purpose of illustrating the claimed invention, and should not be construed so as to limit the scope of the claimed invention.

EXAMPLES

EXAMPLE 1. DOSING GUIDELINES

Dosing of of RSR13 is determined as follows. Table 1 illustrates the RSR13 initial dose schedule.

Table 1
Initial Dose Calculator

Gender	Body weight category	$SpO_2 \geq 93\%$	SpO_2 90-92%
Female	≤ 70 kg	100 mg/kg	75 mg/kg
	> 70 kg	75 mg/kg	75 mg/kg
Male	≤ 95 kg	100 mg/kg	75 mg/kg
	> 95 kg	75 mg/kg	75 mg/kg

Depending upon an individual patient's resaturation time (time required to recover to a stable ≥90% SpO_2 on room air) following RSR13 plus WBRT, supplemental oxygen use may be required for as little as 30 minutes to more than 4 hours. The majority of RSR13 doses in patients with brain metastases from breast cancer required one hour or less of supplemental oxygen after the completion or WBRT. During this period of decreased oxygen saturation, patients require continuous SpO_2 monitoring. If the desired SpO_2 of ≥90% while breathing room air is not achieved, supplemental oxygen is to be continued and increased to a flow of 6–8 L/min, if necessary, until the SpO_2 while breathing room air is stabilized at ≥ 90%.

Dose Modifications - Dosage adjustment is based upon clinical assessments and monitoring of SpO_2 indicating that the patient is experiencing exaggerated effects or toxicities. Table 2 summarizes the RSR13 dose modification schedule.

Table 2
Calculator for Subsequent EXCELAR Doses

Evaluations Prior to Each Treatment Day	EXCELAR Dose
SpO_2 during infusion < 90%	DL-1
Pretreatment SpO_2 < 90%	Omit dose for current treatment day; when SpO_2 ≥90%, resume treatment at DL–1
Hypoxemia temporally associated with other signs/symptoms[a]	DL –1
Renal dysfunction > Grade 1 Common Toxicity Criteria (CTC)[b]	DL –1
Renal dysfunction > Grade 2 CTC[c]	Permanently discontinue EXCELAR
Pretreatment $SpO_2 \geq 93\%$ on room air and ≥90%	DL +1

during EXCELAR infusion on previous day without hypoxemia	

[a]Dyspnea, hypotension/dizziness, renal dysfunction (≥Grade 2 CTC or increase of 1 CTC Grade from baseline);
[b] > Grade 1 CTC or 1 CTC Grade increase from baseline; CTC is based on National Cancer Institute (NCI) Toxicity Criteria scale Version 2.0 published 30 Apr 1999.
[c] > Grade 2 CTC or increase of > 1 CTC Grade from baseline.
DL + 1 Dose increase from 75 mg/kg to 100 mg/kg (max. dose) *no further escalation beyond 100 mg/kg*
DL – 1 Dose reduction from 100 mg/kg to 75 mg/kg, if current dose level is 75 mg/kg *no further reduction beyond 75 mg/kg*, instead omission of dose and resume treatment at 75 mg/kg on Treatment day (RT-day) +1.

RSR13 is administered via parenteral routes of administration, including but not limited to, intravenously , via continuous infusion, subcutaneously, intraperitoneally, intraarterially, transdermally, intramuscularly, via local delivery by catheter or stent, subcutaneously, intraadiposally, intraarticularly, or intrathecally.

EXAMPLE 2. TREATMENT PROTOCOL

Patients with brain metastases were administered RSR13 in a total dose of 0-100 mg/Kg per day based on the dosing guidelines detailed above. In general, RSR13 is administered by intravenous infusion through a central venous access device over 30 minutes at a dose of 75 or 100 mg/kg daily with concurrent supplemental oxygen. Oxygen must be administered at 4 L/min via nasal cannula or facemask beginning 5 minutes prior to initiation of infusion, during infusion and WBRT, and for at least 15 minutes after completion of daily WBRT. RSR13 is administered every day of a fractionated course of WBRT. WBRT must be administered within 30 minutes of the end of the RSR13 infusion.

The patients were given the drug in one dose. RSR13 was administered via central venous access with flow rate controlled by volumetric pump over a 30-45 minute interval with end-infusion no longer than 30 minutes prior to each radiation dose of a 10-day course of WBRT. RSR13 was formulated as a sterile solution for injection and was supplied in single-use glass bottles containing 10 g RSR13 in 500 mL of 0.225% NaCl at a concentration of 20 mg/mL. RSR13 was administered during the 10-day course of WBRT, for a maximum of 10 doses. A control group received radiation and supplemental oxygen only.

Supplemental oxygen is administered at about 4 L/min via nasal cannula beginning about 5 minutes prior to initiation of infusion, during infusion and WBRT, and for at least about 15 minutes after completion of daily WBRT. If the desired SpO_2 of greater than or equal to 90% while breathing room air is not achieved, supplemental oxygen is to be continued and increased to a flow of 6–8 L/min, if necessary, until the SpO_2 while breathing room air is stabilized at greater than or equal to 90%.

Data obtained in the controlled study confirmed the previously suggested safety profile of RSR13 as sole adjunct to radiation therapy in the treatment of cancer patients. The majority of treatment-emergent adverse events were Grade 1 or 2 in severity, resolved spontaneously or within the duration of the study, and responded well to concomitant treatment with antiemetics for nausea/vomiting, nonsteroidal anti-inflammatory drugs for headache, supplemental oxygen for hypoxemia. While the most commonly reported Grade 3 adverse event in RSR13-treated patients was hypoxemia (reported in 11% of patients), no Grade 4 hypoxemia was reported. Muscle weakness and dyspnea (reported in 3% of patients) were the most commonly reported Grade 3 adverse events in Control patients and both events were reported as a Grade 4 event in 1 patient each. The most commonly reported Grade 4 adverse event in both treatment and control groups was disease progression (reported in 6% of both groups).

EXAMPLE 3. PHARMACOKINETICS

Plasma and red blood cell (RBC) drug concentration assayed on 2 days during the course of RSR13 administration: WBRT day 1 (end-infusion) and on 1 single day between WBRT days 6 and 10 (pre-infusion and end-infusion assays). Regression analysis was used to explore the relationship between trough and peak concentrations and continuous clinical covariates (eg, age, serum albumin, hematocrit, serum creatinine, etc). No clinically relevant drug accumulation occurred based on WBRT week 2 preinfusion RSR13 concentrations in RBCs. A dose of RSR13 was considered serviceable if it achieved a sufficient PK (> 483μg/ml), and corresponds to a predicted p50 shift of 10 mmHg.

There was a proportional increase in the RSR13 concentrations in RBCs for patients dosed at 75 or 100 mg/kg. Patients with higher body weight had higher RSR13

concentrations in RBCs than low weight patients at a given dose. For all RSR13-treated patients, those with a dose change had a higher RSR13 concentration in RBCs at the initial dose of 100 mg/kg than patients who had a starting dose of 100 mg/kg with no dose change. RSR13 concentrations in RBCs were higher in breast primary patients than patients with NSCLC and other primary because there were a higher proportion of high body weight breast primary patients. RSR13 concentrations in RBCs were comparable for NSCLC patients at 100 mg/kg and breast patients at 75 mg/kg, but the RSR13 concentrations in RBCs for NSCLC patients at 75 mg/kg were substantially lower in breast patients at 75 mg/kg. These analyses reveal that patients with RSR13 concentrations in RBCs that reached optimal levels had a better outcome than those patients who did not. A clear correlation between PK, number of RSR13 doses, and MST was established.

	Control		RSR13		
Patients	< 7 WBRT Doses MST (n)	≥7 WBRT Doses MST (n)	< 7 RSR13 Doses MST (n)	≥7 RSR13 Doses < 7 Successful [(a)] MST (n)	≥7 RSR13 Doses/≥ 7 Successful [(a)] MST (n) p value (b)
All	0.71 (10)	4.47 (257)	2.96 (53)	4.93 (118)	6.90 (100) 0.001
NSCLC	0.66 (4)	4.47 (147)	2.71 (30)	4.73 (65)	6.83 (53) 0.0011
Breast	Unk. (2)	4.57 (53)	3.52 (13)	7.33 (22)	25.72 (25) 0.0002
(a): a dose of RSR13 was considered successful if it achieved a sufficient PK (> 483 μg/ml); this corresponds to a predicted p50 shift of 10 mmHg (b): vs Control ³ 7 WBRT doses MST: median survival time					

EXAMPLE 5. EFFICACY

A. Patient Survival. One measurement of efficacy is the survival in total patient population. For eligible patients, the observed mean survival time for the control group was 4.37 months as compared to 5.39 months for the RSR13 treated group.

In patients with breast as the site of primary, there was a highly statistically significant difference detected for the survival distribution function in the treatment

versus the control group (HR = 0.552, p = 0.0061). Analyses showed consistent results for breast cancer patients across all pre-specified covariates.

The estimated increase in response rate in all patients randomized to the RSR13 group was 7.9% (95% CI: –0.4%-16.3%) compared to the Control group (p = 0.0609). In breast primary patients, logistic multiple regression showed RSR13 treatment effect to be statistically significant for predicting response (p = 0.0209). The increase in response rate translated into prolonged survival.

B. Radiographic Tumor Progression. Radiographic progression is defined by radiographic criteria only, based on a blinded central review. Determination of radiographic tumor progression in the brain was based on contrast enhanced MRI or CT scans taken at screening and compared to follow-up scans taken 1 month after the end of WBRT, 3 months after the end of WBRT, and every 3 months thereafter until death. Maximum bi-dimensional measurements (x = transverse, y = antero-posterior) were used to compute the bi-dimensional product and for determination of response and radiographic progression. Time to radiographic tumor progression in the brain was reported by means of Kaplan-Meier estimates. Gray's test (Gray R. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Annals of Statistics 1998;16:1141-1154) was used to compare cumulative incidence between treatment and control groups. Potential competing risks for radiographic progression in the brain included death without progression and loss to follow-up. The date of tumor progression is defined as the date of radiographic documentation that any treated lesion in the brain is enlarged by more than 25% in the bi-dimensional product. The reference to "any treated lesion" mans that the lesion was present prior to RT.

The estimated increase in response rate in all patients randomized to the RSR13 group was 7.9% (95% CI: –0.4%-16.3%) compared to the Control group (p = 0.0609). In breast primary patients, logistic multiple regression showed RSR13 treatment effect to be statistically significant for predicting response (p = 0.0209). The increase in response rate translated into prolonged survival.

C. Quality of Life. Quality of life was determined by means of the Spitzer Questionnaire (SQ) and Karnofsky Performance Status (KPS) assessment. The tests were performed at baseline, at WBRT day 10, and at all routine follow-up visits. A sustained

drop in the KPS score to less than 60 was defined as a significant drop. The 5 questions comprising the Spitzer Questionnaire were weighted evenly. For each evaluation with at least 3 out of 5 questions answered, an average score was computed for each patient. Questionnaires with fewer than 3 questions answered were treated as missing data. The protocol specified a sustained drop in the Spitzer Questionnaire score of 2 points constituted a significant drop.

Comparisons of QOL measures between treatment and control groups focused on 1-month, 3-month, 6-month, and 1-year follow-up time-points and did not include WBRT day 10.

There was a highly statistically significant percentage of patients with stable or improving KPS scores over time in the RSR13 group versus the Control group ($\chi^2 = 9.0096$, $p = 0.0027$) ().

Table
Numbers and Percentages of All Randomized Patients with Stable or Improving KPS Scores over Time in Study RT-009[a]

Time	Control (N = 267) n (%)	RSR13 (N = 271) n (%)
1 month	96 (36)	119 (44)
3 months	49 (18)	64 (24)
6 months	39 (15)	49 (18)
12 months	10 (4)	19 (7)

[a]$p = 0.0027$, Cochran-Mantel-Haenszel test with time (1, 3, 6, and 12 months) as strata

There was a trend toward a higher percentage of patients with stable or improving SQ scores over time in the RSR13 group versus the Control group ($\chi^2 = 3.4675$, $p = 0.0626$) ().

Table
Numbers and Percentages of All Randomized Patients with Stable or Improving SQ Scores over Time in Study RT-009[a]

Time	Control (N = 267) n (%)	RSR13 (N = 271) n (%)
1 month	98 (37)	115 (42)
3 months	55 (21)	62 (23)
6 months	39 (15)	43 (16)
12 months	15 (6)	24 (9)

[a]$p = 0.0626$, Cochran-Mantel-Haenszel test with time (1, 3, 6, and 12 months) as strata

For patients with breast primary, there was a statistically significant difference detected in the distribution of KPS score categories between treatment groups at 6 months and 1 year ($p = 0.0046$ and $p = 0.0070$, respectively).

CLAIMS

What is claimed is:

1. A method of treating a central nervous system metastatic cancer sensitive to the combination of radiation, supplemental oxygen, and RSR13 in a host having a central nervous system metastatic cancer comprising:

administering radiation to the host;

administering RSR13 to the host, and

administering supplemental oxygen to the host,

wherein the radiation, supplemental oxygen, and RSR13 are administered in amounts effective to cause an arrest or regression of the central nervous system cancer in the host.

2. A method of treating a central nervous system metastatic cancer sensitive to the combination of radiation, supplemental oxygen, and RSR13 in a host having a central nervous system metastatic cancer comprising:

A) administering radiation to the host;

B) administering RSR13 to the host, wherein the RSR13 is administered at a dosage selected from the group consisting of

i) 100 mg/kg, if conditions are conditions selected from the group consisting of:

a) RT day 1, the host is a male $\leq$ 95 kg, and SpO_2 is $\geq$ 93%

b) RT day 1, the host is a female $\leq$ 70 kg, and SpO_2 is $\geq$ 93%

c) RT day 2-10, the dose was 75 mg/kg on the previous dosing day, and SpO_2 while breathing room air is currently $\geq$ 93% and no adverse event occurred on the previous dosing day, wherein said adverse event is selected from the group consisting of supplemental oxygen administration > 3 hours after end-infusion of RSR13 before SpO2 while breathing room air returned to $\geq$ 90% on the previous dosing day, the patient experienced nausea and/or vomiting (grade 2 or higher) or clinically significant hypotension (investigator judgment) associated with RSR13 within 12 hours after RSR13 administration on the previous dosing day, and the patient developed hypoxemia which

required treatment after discharge on the previous dosing day;

d) RT day 2-10, SpO_2 is >90%, the dose was 100 mg/kg on the previous day and no adverse event occurred on the previous day, wherein said adverse event is selected from the group consisting of supplemental oxygen administration > 3 hours after end-infusion of RSR13 before SpO2 while breathing room air returned to ≥ 90% on the previous dosing day, the patient experienced nausea and/or vomiting (grade 2 or higher) or clinically significant hypotension (investigator judgment) associated with RSR13 within 12 hours after RSR13 administration on the previous dosing day, the patient developed hypoxemia which required treatment after discharge on the previous dosing day, and SpO_2 while breathing room air is 90-92% but was ≥ 93% on the previous dosing day;

ii) 75 mg/kg, if conditions are conditions selected from the group consisting of:

a) RT day 1, the host is a male > 95 kg, and SpO_2 is ≥ 93%,

b) RT day 1, the host is a female > 70 kg, and SpO_2 is ≥ 93%,

c) RT day 1 and SpO_2 is 90-92%,

d) RT day 2-10, the previous day's dose was held, SpO_2 is 90-92% and SpO_2 was 90-92% on the dosing day that led to holding the RSR13 dose,

e) RT day 2-10, the previous day's dose was held, and SpO_2 is ≥ 93%,

f) RT day 2-10, the previous day's dose was 100 mg/kg, and an adverse event occurs, wherein said adverse event is selected from the group consisting of supplemental oxygen administration > 3 hours after end-infusion of RSR13 before SpO2 while breathing room air returned to ≥ 90% on the previous dosing day, the patient experienced nausea and/or vomiting (grade 2 or higher) or clinically significant hypotension (investigator judgment) associated with RSR13 within 12 hours after RSR13 administration on the previous dosing day, the patient developed hypoxemia which required treatment after discharge on the previous dosing day, and SpO_2 while breathing room air is 90-92% but was ≥ 93% on the previous dosing day, and

g) RT day 2-10, SpO_2 is >90%, and the dose was 75 mg/kg on the previous day and no adverse event occurred on the previous day, wherein said adverse

event is selected from the group consisting of supplemental oxygen administration > 3 hours after end-infusion of RSR13 before SpO2 while breathing room air returned to ≥ 90% on the previous dosing day, the patient experienced nausea and/or vomiting (grade 2 or higher) or clinically significant hypotension (investigator judgment) associated with RSR13 within 12 hours after RSR13 administration on the previous dosing day, the patient developed hypoxemia which required treatment after discharge on the previous dosing day, and SpO_2 while breathing room air is 90-92% but was ≥ 93% on the previous dosing day; and

iii) 0 mg/kg, if conditions are conditions selected from the group consisting of:

a) SpO_2 is < 90%,

b) RT day 2-10, the dose was 75 mg/kg on the previous day and an adverse event occurs, wherein said adverse event is selected from the group consisting of supplemental oxygen administration > 3 hours after end-infusion of RSR13 before SpO2 while breathing room air returned to ≥ 90% on the previous dosing day, the patient experienced nausea and/or vomiting (grade 2 or higher) or clinically significant hypotension (investigator judgment) associated with RSR13 within 12 hours after RSR13 administration on the previous dosing day, the patient developed hypoxemia which required treatment after discharge on the previous dosing day, and SpO_2 while breathing room air is 90-92% but was ≥ 93% on the previous dosing day ,

c) RT day 2-10, the dose was 0 mg/kg on the previous day, SpO_2 is 90-92% but had been ≥ 93% on the previous dosing day that led to holding RSR13

d) RT day 2-10, SpO_2 is >90%, and the dose was 0 mg/kg on the previous day and an adverse event occurs, wherein said adverse event is selected from the group consisting of supplemental oxygen administration > 3 hours after end-infusion of RSR13 before SpO2 while breathing room air returned to ≥ 90% on the previous dosing day, the patient experienced nausea and/or vomiting (grade 2 or higher) or clinically significant hypotension (investigator judgment) associated with RSR13 within 12 hours after RSR13 administration on the previous dosing day, the patient developed hypoxemia which required treatment after discharge on the previous dosing day, and SpO_2 while breathing room air is 90-92% but was ≥ 93% on the previous dosing day; and

C) administering supplemental oxygen to the host,

wherein the radiation, supplemental oxygen, and RSR13 are administered in amounts effective to cause an arrest or regression of the central nervous system cancer in the host.

2. The method of claim 1 or 2, wherein the metastatic cancer is derived from a primary cancer selected from the group consisting of lung, breast, melanoma, renal, and colon .

3. The method of claim 1 or 2, wherein the radiation is administered in at least about 3 Gray (Gy) fractions at least once every day for ten days to a treatment volume.

4. The method of claim 1 or 2, wherein the radiation is administered in fractions, wherein 10 fractions are administered to an initial treatment volume.

5. The method of claim 1 or 2, wherein a total of at least about 30 Gy of radiation is administered to the host.

6. The method of claim 1 or 2, wherein radiation is administered to a whole brain of the host.

7. The method of claim 1 or 2, wherein the RSR13 is administered via a route selected from the group consisting of intravenously, continuous infusion, subcutaneously , intraperitoneally, intraarterially, transdermally, intramuscularly, via local delivery by catheter or stent, subcutaneously, intraadiposally, intraarticularly, or intrathecally.

8. The method of claim 1 or 2, wherein the RSR13 is administered at an initial dosing level of at least about 75 mg/Kg/day.

9. The method of claim 1 or 2, wherein the RSR13 is administered so as to achieve a PK of greater than about 483μg/ml.

ABSTRACT

Disclosed is a method of treating a cancer of the central nervous system in a host including administering radiation to the host; and administering efaproxiral sodium (RSR13) to the host; wherein the radiation and efaproxiral sodium are administered in amounts effective to cause the arrest or regression of the cancer of the central nervous system in the host.

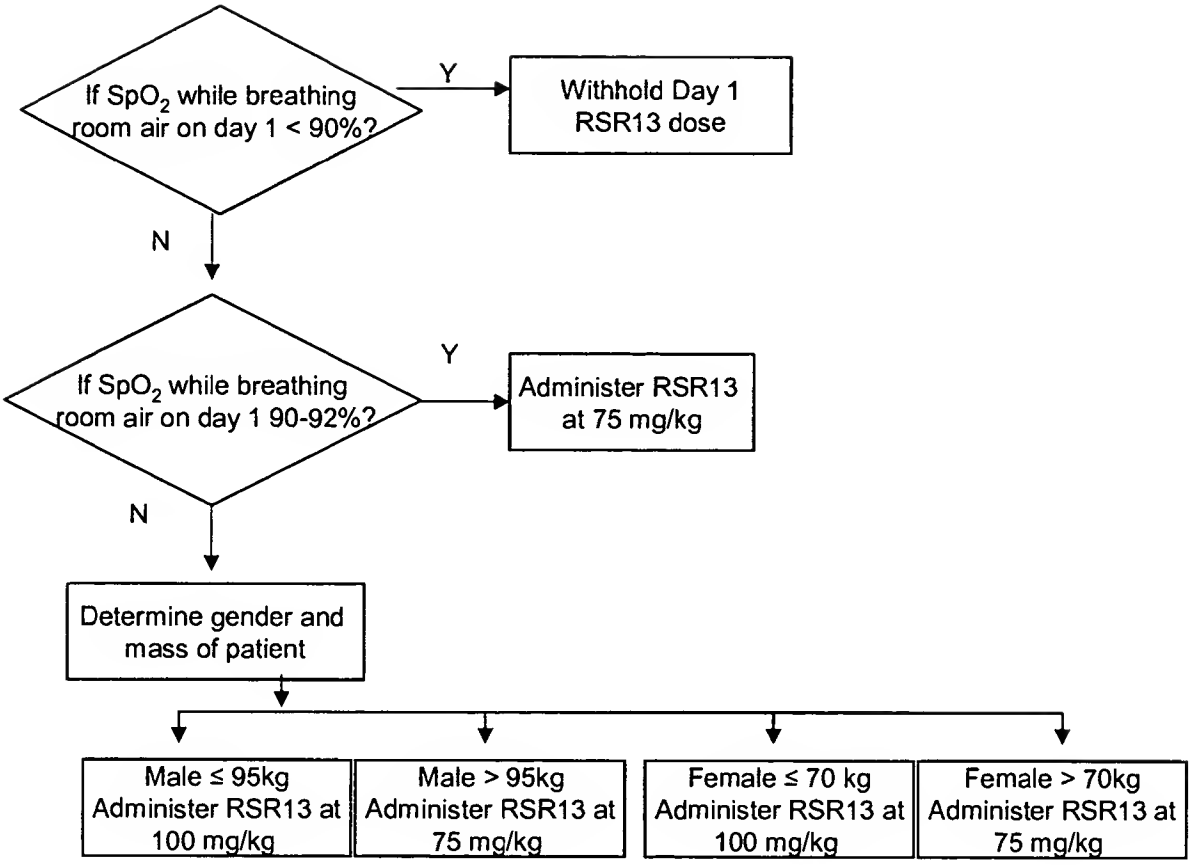

If SpO_2 while breathing room air on day 1 < 90%?
Y
Withhold Day 1 RSR13 dose
N
If SpO_2 while breathing room air on day 1 90-92%?
Y
Administer RSR13 at 75 mg/kg
N
Determine gender and mass of patient
Male ≤ 95kg Administer RSR13 at 100 mg/kg
Male > 95kg Administer RSR13 at 75 mg/kg
Female ≤ 70 kg Administer RSR13 at 100 mg/kg
Female > 70kg Administer RSR13 at 75 mg/kg

Figure 1

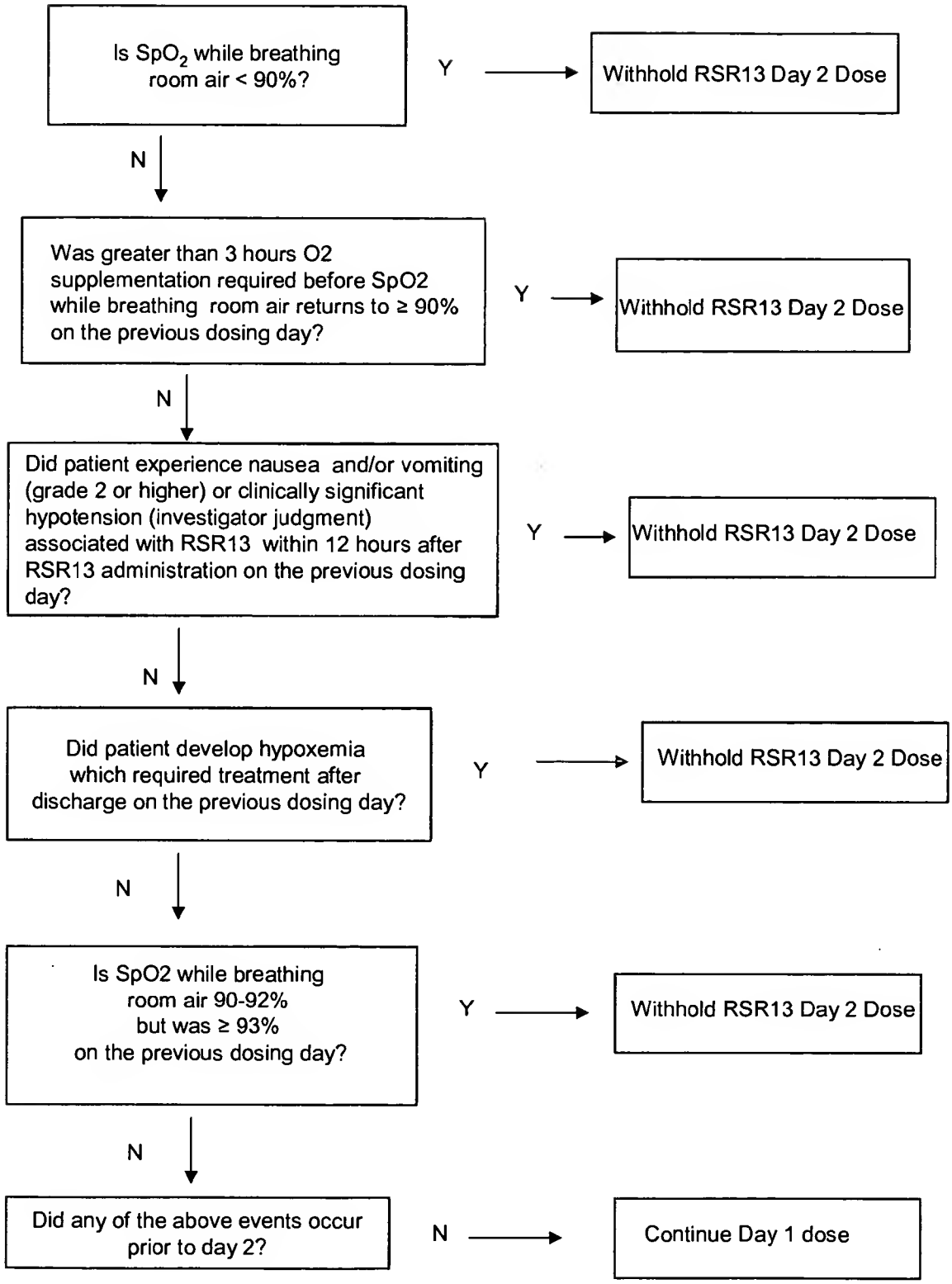

Is SpO_2 while breathing room air < 90%?
Y
Withhold RSR13 Day 2 Dose
N
Was greater than 3 hours O2 supplementation required before SpO2 while breathing room air returns to ≥ 90% on the previous dosing day?
Y
Withhold RSR13 Day 2 Dose
N
Did patient experience nausea and/or vomiting (grade 2 or higher) or clinically significant hypotension (investigator judgment) associated with RSR13 within 12 hours after RSR13 administration on the previous dosing day?
Y
Withhold RSR13 Day 2 Dose
N
Did patient develop hypoxemia which required treatment after discharge on the previous dosing day?
Y
Withhold RSR13 Day 2 Dose
N
Is SpO2 while breathing room air 90-92% but was ≥ 93% on the previous dosing day?
Y
Withhold RSR13 Day 2 Dose
N
Did any of the above events occur prior to day 2?
N
Continue Day 1 dose

Figure 2

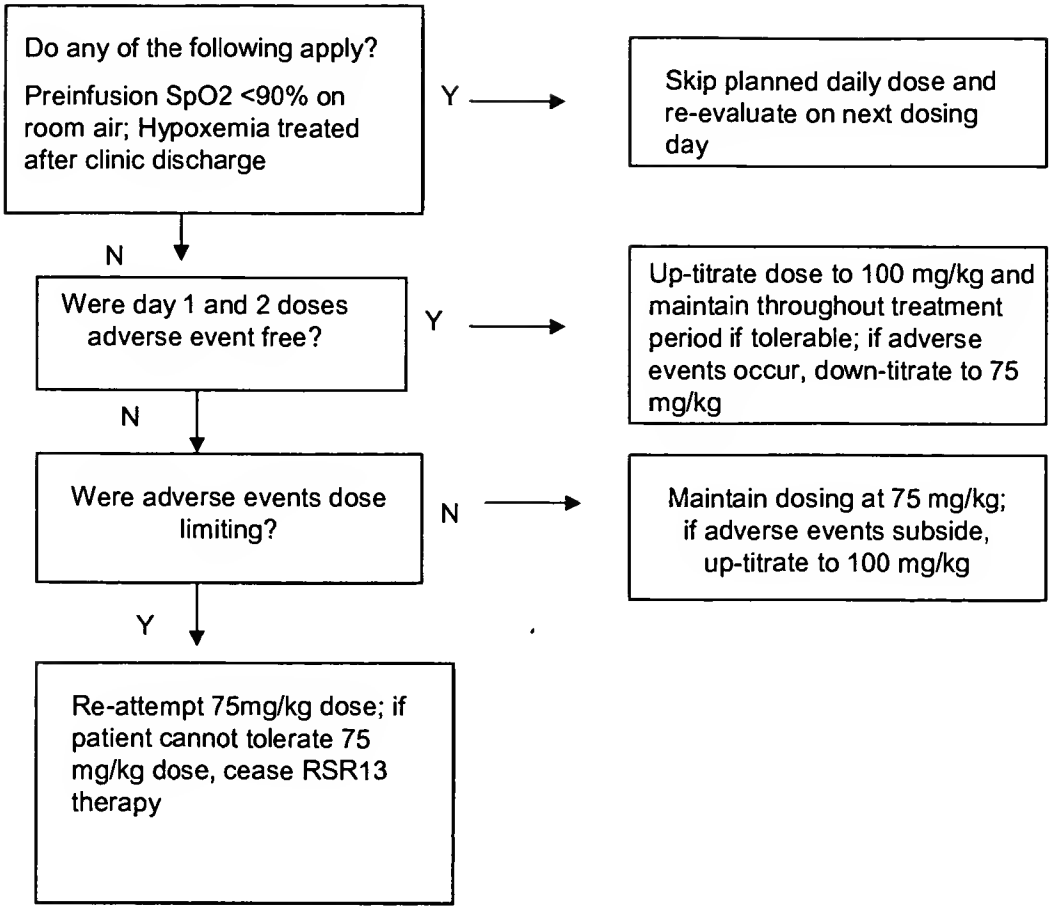

Do any of the following apply?
Preinfusion SpO2 <90% on room air; Hypoxemia treated after clinic discharge
Y
Skip planned daily dose and re-evaluate on next dosing day
N
Were day 1 and 2 doses adverse event free?
Y
Up-titrate dose to 100 mg/kg and maintain throughout treatment period if tolerable; if adverse events occur, down-titrate to 75 mg/kg
N
Were adverse events dose limiting?
N
Maintain dosing at 75 mg/kg; if adverse events subside, up-titrate to 100 mg/kg
Y
Re-attempt 75mg/kg dose; if patient cannot tolerate 75 mg/kg dose, cease RSR13 therapy

Figure 3